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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,875	04/30/2001	Kenneth S. Zuckerman	0152.00393	8728

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/03/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,875	ZUCKERMAN ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-20* is/are pending in the application.

4a) Of the above claim(s) *4,14 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-13,15-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 since the brief description of the drawings/figures (pages 3-5 of the instant specification) does not contain the SEQ ID NOS. of the nucleic acid sequences found in the drawings/figures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132. Applicant's response to this Office action will be considered non-responsive if the sequence rules are not met.

2. The specification is objected to for grammatical/typographical error(s) on page 3, line 15.

Information Disclosure Statement

3. The information disclosure statement filed 08/31/01 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The IDS has been considered for all the references except those marked B, E, G-J, L, N, P, Q, Y, Z and AA, since a copy of these references was not supplied with the IDS.

Drawings

4. The drawings filed 04/30/01 have been approved by an Official draftsman.

Election/Restriction

5. Applicant's election with traverse of Group II, in Paper No. 11, filed 11/25/2002, is acknowledged. Group II is now considered to encompass claims 1-3, 6-13 and 15-17 and 19-20, since claim 18 is dependent on claim 14. In a telephone message left by applicants' representative, Amy Rinaldo on February 6, 2003, permission was granted to withdraw claim 18 from Group II.

The traversal is on the ground(s) that "[a]ll of the groups of claims relate to methods including administering oligonucleotides to inhibit a transcription factor, and moreover, all are classified in the same class. The only different between groups is that different factors are being inhibited. The search required for one group would therefore necessarily be the same search required for the other groups because all of the groups are directed to methods including administering oligonucleotides to inhibit transcription factors. Since there is a great amount of cross-classification amongst the sub-classes in this class, it is respectfully submitted that examination of all claims in a single application would be efficient...."

This is not found persuasive because the instant restriction was a lack of unity restriction, and not a restriction based on U.S. practice. As argued in the lack of unity mailed 0925/02, the instantly claimed compositions did not share a common core structure, since each

oligonucleotide claimed has a unique nucleic acid sequence. The oligonucletotides claimed where thus restrictable on that basis.

The requirement is still deemed proper and is therefore made FINAL.

6. Claims 4, 14 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11, filed 11/25/2002.

Claim Objections

7. Claim 3 contains a grammatical error in line 2, "modulating the *functional of* the STAT family...." It appears that the claim should read: "modulating the function of the STAT family...."

8. Claim 15 contains a grammatical error in line 3: "an oligonucleotides". It appears that the claim should read "an oligonucleotide".

9. Claim 17 has a typographical error: the "the" at the start of the claim needs to be capitalized.

Claim Rejections - 35 USC § 112

10.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-12 lack antecedent basis since claim 9 is dependent on itself.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 2, 3, 6, 7, 8, 13, 15, 16, 17 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administration of the claimed decoy oligonucleotides to cells in cell culture for the decreased (inhibited) function of transcription factor(s) which bind the administered oligonucleotides, does not reasonably provide enablement for methods of administration and/or treatment of a whole organism patients by administration of the claimed oligonucleotide decoys so that the function of the transcription factor(s) which bind the claimed oligonucleotides are modulated (unregulated or inhibited) in the

whole organism for modulation and/or treatment effects. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a method of modulating the function of transcription factors by administering an effective amount of an oligonucleotide containing optimal nucleotide binding sites for the transcription factor. Claim 2 specifies the method of claim 1, wherein said administering step further includes administering an effective amount of an oligonucleotide for downregulating the function of transcription factors. Claim 3 specifies the method according to claim 1, wherein said modulating step includes modulating the function[al] of the STAT family of transcription factors by administering an effective amount of an oligonucleotide containing optimal binding sites for the STAT family of transcription factors.

Claim 6 is drawn to a treatment for patients having illnesses in which activation of transcription factors play a role by administering to a patient an effective amount of an oligonucleotide which competitively binds a transcription factor of the related illness. Since the claim contains an active step of administering to a patient an oligonucleotide, the claim, drawn to a treatment, is treated on the merits herein as a method of treatment claim.

Claim 7 is drawn to a method of inhibiting a transcription factor in a cell by administering an effective amount of a double stranded oligonucleotide, the oligonucleotide having a sequence bound by the transcription factor.

Claim 16 is drawn to a method of inhibiting malignant proliferation by administering an effective amount of a double stranded oligonucleotide, the oligonucleotide having a sequence bound by a transcription factor, the transcription factor activity being correlated to malignant proliferation.

Claim 8 is drawn to a pharmaceutical composition for inhibiting a transcription factor in a cell comprising an effective amount of a double stranded oligonucleotide, said oligonucleotide having a sequence bound by a transcription factor. Claim 13 is drawn to the pharmaceutical composition according to claim 8, wherein said transcription factor is STAT5 and said oligonucleotide contains the sequence TTCNNNGAA, in which "N" is any nucleotide. Claim 15 is drawn to the pharmaceutical composition according to claim 13, wherein said oligonucleotide is selected from the group comprising an oligonucleotide[s] having the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).... Since "pharmaceutical compositions" have implied therapeutic use, and administration to a whole organism, they are included in the instant rejection. Note that should the claims be amended to remove the word "pharmaceutical" from the preamble, this action would be sufficient to overcome the instant rejection.

Claim 20 is drawn to a therapeutic agent comprising an effective amount of an oligonucleotide for modulating the function of transcription factors and a pharmaceutically acceptable carrier. Claim 17 is drawn to the therapeutic agent according to claim 20, wherein said effective amount is an effective amount of the oligonucleotide of claim 13 for modulating the function of transcription factors and a pharmaceutically acceptable carrier. Since claims 20

and 17 are drawn to "therapeutic agents" they are examined on the basis of their functional language herein. Note that should the claims be amended to remove the word "therapeutic" from the preamble, this action would be sufficient to overcome the instant rejection.

The specification as filed taught on page 26, lines 19-32, that addition of the double stranded 20-mer oligodeoxynucleotide was containing the STAT5 binding sequence (TTCCCCGAA) to HEL/Dami cells in cell culture. Applicants found that the "specific TTCCCCGAA-containing double-stranded oligonucleotide inhibits the survival and proliferation of the HEL/Dami and Mef-01 cell lines, whereas the non-specific oligonucleotide does not inhibit specifically the survival and proliferation of these cells." The HEL/Dami cells are a malignant, leukemic cell line, and the administration of the STAT5 decoy resulted in death of the leukemic cells (page 27, line 1). The specification further teaches prophetically administration of the STAT5 decoys to cancer cells in mice and pharmaceutical compositions of the STAT5 decoys for cancer treatment purposes (see pages 29-31, and 13-16 of the specification as filed).

The teachings of Victor J. Dzau in an editorial review of transcription factor decoys show that there are unpredictable factors in the use of such transcription factor decoys for therapeutic uses. They teach on page 1235, col. 1, lines 3-55, that the unpredictable factors are the specificity of the TFD, the stability of the TFD, the efficiency of tissue/cellular delivery, the breath of treatment effects desired (to many tissues, or select tissues), intracellular stability of the TFD and resistance to endonuclease digestion, and timing of the treatment. These unpredictable factors for delivery of the double-stranded TFD oligonucleotides parallel the unpredictabilities

found in the related art of antisense administration to cells in a whole organism versus administration to cells in cell culture.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical

translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who

teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed TFD molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art of both TFDs (Dzau's teachings) as well as the art of antisense administration. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of TFD oligonucleotide molecules in whole organisms. Specifically the specification does not teach (1) stability of the TFD molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by

the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Furthermore, since neither the specification nor the prior art taught increasing the function of the transcription factors by using the TFDs, one of skill in the art would only have been enabled for decreasing the function of the transcription factor which binds the decoy sequence, but not the breath of any modulation of the transcription factors, which embraces both increasing and decreasing the function. Since it is unclear how sequestering the transcription factor on a decoy, would act to increase the function of the transcription factor, one of skill in the art would necessarily practice "trial and error" experimentation to make and use the claimed methods for modulation of transcription factor function since as such modulation embraces increasing transcription factor function. Absent further guidance in the specification as filed for increasing the function of transcription factors using the TFDs, one of skill in the art would necessarily practice undue experimentation to make and use the claimed invention .

14. Claims 1-3, 6-13, 15-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

See the description of the claims above. Claim 19 is further drawn to methods of removing malignant cells in vitro by exposing a cell culture to an effective amount of oligonucleotide containing optimal nucleotide binding sites for a transcription factor.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims lack written description since the claims are drawn to methods of treatment and downregulation of any transcription factor for functions such as removing malignant cells from a cell culture and inhibiting malignant proliferation, as well as any treatment of a patient having an illness. The functional use of the claimed TFDs for treatment, requires a knowledge of

the described disease states which are treated upon administration of the claimed compounds. The invention thus rests on the correlation of a desired treatment function to the claimed and disclosed therapeutic compounds. The specification as filed, however, does not teach any specific identifying design characteristics of any TFD oligonucleotide having a clear inhibition of a specific TFD in any whole organism environment such that the functions of treatment are achieved. In the absence of a more specific description of the design criteria (ie., specific sequences, modifications, routes of administration, formulation) needed to visualize a representative number of species of any such TFD effective for treatment or decreasing or removing malignancies as claimed and a specific nexus to the therapeutic results achieved in a particular disease environment in a particular whole organism, one of skill in the art would not have sufficient written description of the claimed compounds. It was art recognized at the time the invention was made that specific features of drugs to target a specific biomolecule such as a transcription factor *in vivo*, and specifically, features which would deliver the molecule to the appropriate location in the whole organism, avoid undue toxicity, and features which would have an expectation to stabilize the molecule for functional use in a whole organism were highly unpredictable in the art and not available to the skilled artisan based on knowledge of the target molecule structure. Therefore, the specification as filed does not show that Applicants' were in possession of (the knowledge of) a representative number of TFD compounds at the time the invention was made to teach possession of the invention having the claimed functional limitations.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 2, 3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (Abstract presented Monday, August 25, 1997, at the 26th Annual Meeting of the International Society for Experimental Hematology in Cannes, France, August 24-28, 1997, and published in *Experimental Hematology*, Vol. 25, No. 8, p. 764, 1997).

Claim 1 is drawn to a method of modulating the function of transcription factors by administering an effective amount of an oligonucleotide containing optimal nucleotide binding sites for the transcription factor. Claim 2 specifies the method of claim 1, wherein said administering step further includes administering an effective amount of an oligonucleotide for downregulating the function of transcription factors. Claim 3 specifies the method according to claim 1, wherein said modulating step includes modulating the function[al] of the STAT family of transcription factors by administering an effective amount of an oligonucleotide containing optimal binding sites for the STAT family of transcription factors. Claim 7 is drawn to a method of inhibiting a transcription factor in a cell by administering an effective amount of a double

stranded oligonucleotide, the oligonucleotide having a sequence bound by the transcription factor.

Liu et al. (Applicants' own work) taught administration of a STAT5 decoy to Dami/HEL and Meg-01 factor-independent leukemic cell lines and downregulation of the JAK2/STAT5 signaling transduction pathway (downregulation of the STAT5) which is constitually activated in the Dami/HEL cells. They thus taught the claimed methods of administering the double-stranded transcription factor decoy to cells which binds the STAT5 transcription factor and downregulates its function.

17. Claims 1, 2, 3, 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Boccaccio et al. (Nature, Vol. 391, 1/15/98, pp. 285-288).

Claim 1 is drawn to a method of modulating the function of transcription factors by administering an effective amount of an oligonucleotide containing optimal nucleotide binding sites for the transcription factor. Claim 2 specifies the method of claim 1, wherein said administering step further includes administering an effective amount of an oligonucleotide for downregulating the function of transcription factors. Claim 3 specifies the method according to claim 1, wherein said modulating step includes modulating the function[al] of the STAT family of transcription factors by administering an effective amount of an oligonucleotide containing optimal binding sites for the STAT family of transcription factors. Claim 7 is drawn to a method of inhibiting a transcription factor in a cell by administering an effective amount of a double

stranded oligonucleotide, the oligonucleotide having a sequence bound by the transcription factor.

Boccaccio et al. taught that making an h-SIE decoy of the sequence 5'-CATTTCCCGTAAATC-3' (page 288, col. 1), which binds STAT (p. 287, Figure 3 legend, line 1) and administration to MDCK, GTL 16, and MLP29 epithelial cell cultures (page 287, col. 2, methods, lines 1-3) for inhibition of the STAT transcription factor functions and decreasing growth of epithelial tubules (page 286, col. 2, lines 26-29).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. Or Boccaccio et al. in view of Bard et al. (U.S. Patent 6,448,011).

Claim 8 is drawn to a pharmaceutical composition for inhibiting a transcription factor in a cell comprising an effective amount of a double stranded oligonucleotide, said oligonucleotide having a sequence bound by a transcription factor.

Liu et al. is relied upon as set forth above to have taught administration of a STAT5 decoy to Dami/HEL and Meg-01 factor-independent leukemic cell lines and downregulation of the JAK2/STAT5 signaling transduction pathway (downregulation of the STAT5) which is constitually activated in the Dami/HEL cells. They thus taught the claimed methods of administering the double-stranded transcription factor decoy to cells which binds the STAT5 transcription factor and downregulates its function. They did not specifically teach administration of the STAT5 double stranded oligonucleotide with a pharmaceutical carrier, ie. as a pharmaceutical composition.

Boccaccio et al. taught that making an h-SIE decoy of the sequence 5'-CATTTCCCGTAAATC-3' (page 288, col. 1), which binds STAT (p. 287, Figure 3 legend, line 1) and administration to MDCK, GTL 16, and MLP29 epithelial cell cultures (page 287, col. 2, methods, lines 1-3) for inhibition of the STAT transcription factor functions and decreasing growth of epithelial tubules (page 286, col. 2, lines 26-29). They did not specifically teach administration of the STAT double stranded oligonucleotide with a pharmaceutical carrier, ie. as a pharmaceutical composition.

Bard et al. (U.S. Patent 6,448,011) is relied upon to teach in col. 24, lines 6-11) that "the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents."

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have practiced the method of Liu et al., administration of the STAT5 decoy, to the Dami/HEL cells in cell culture with a "pharmaceutically acceptable carrier" as defined by Bard et al., since any type of wetting agent, water, buffers or emulsions, would have been acceptable as agents for making a pharmaceutical composition of the STAT5 decoy. Similarly, it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have practiced the method of Boccaccio et al., administration of the STAT decoy, to the epithelial cells in cell culture with a "pharmaceutically acceptable carrier" as defined by Bard et al., since any type of wetting agent, water, buffers or emulsions, would have been acceptable as agents for making a pharmaceutical composition of the STAT decoy.

One of ordinary skill in the art would have been motivated to administer either the STAT5 decoy of Liu et al. or the STAT decoy of Boccaccio et al. to cells in cell culture using a wetting agent taught by Bard et al., such as a buffer, since nucleic acid oligonucleotides such as the double-stranded STAT5 oligonucleotide, are more stably transduced into cells in cell culture in solution.

One of ordinary skill in the art would have had an expectation of success to make the claimed pharmaceutical composition of the STAT5 oligonucleotide of Liu et al. or the STAT decoy of Boccaccio et al. with a buffer for administration to cells in cell culture since Bard et al. taught that use of wetting agents such as water and buffers is commonly acceptable as a carrier for pharmaceutical compositions.

20. Claims 6, 16, 17, 19 and 20 are free of the prior art since the prior art did not teach nor fairly suggest use of the STAT or other transcription decoys for treatment of cancer malignancies or other diseases either in vitro or in a whole organism. Claims 13 and 15 are further free of the prior art because the closest prior art, WO 95/28482 and U.S. Patent 5,712,094, taught the STAT recognition motifs (such as in claim 13), but did not teach use of such regions for decreasing the function of the STAT transcription factors as oligonucleotide decoys, but rather taught use of the regions in vector compositions for increasing cytokine mediated regulation of gene expression and increasing transcription of linked nucleic acids.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor,, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

SEAN McGARRY
PRIMARY EXAMINER

M. M. Schmidt
February 10, 2003